



National Institute of
Environmental Health Sciences



Environmental Epidemiology of Autism Risk Network (EEARN) Meeting

Thursday, May 2, 2019

**Le Westin Montreal
270 Saint-Antoine Ouest
Canada**

**Hosted by the
National Institute of Environmental Health Sciences
and Autism Speaks**

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Agenda



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Thursday, May 2, 2019

Le Westin Montreal
Montreal A-B – 11e étage
270 Saint-Antoine Ouest
Canada

Agenda

- 6:00 p.m. **Registration**
Refreshments, Donated by Autism Speaks
- 7:00 p.m. **Welcome and Introduction**
Cindy Lawler, National Institute of Environmental Health Sciences (NIEHS)
- 7:10 p.m. **Machine Learning and Risk Factor Epidemiology**
Youssef Oulhote, University of Massachusetts Amherst
- 7:40 p.m. **Panel Discussion and Q&A with Youssef Oulhote on Machine Learning and Risk Factor Epidemiology**
Moderator: Alan Brown, Columbia University

Panelists:
Dheeraj Raj, University of Bristol
Amy Kalkbrenner, University of Wisconsin-Milwaukee
Nathaniel Snyder, Drexel University
- 8:40 p.m. **Poster Session**
- 9:10 p.m. **Discussion — EEARN 2020**
Moderators: Astrid Haugen, NIEHS
Amanda Garton, NIEHS
- 9:25 p.m. **Closing**
Cindy Lawler, NIEHS
- 9:30 p.m. **Adjourn**

Hosted by the National Institute of Environmental Health Sciences and Autism Speaks



Poster Abstracts

Poster Abstracts

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1 Neonatal Thyroid Stimulating Hormone and Subsequent Diagnosis of Autism Spectrum Disorders and Intellectual Disability

Jennifer Ames, Kaiser Permanente Division of Research

Abstract:

Background: Hypothyroid conditions in early life, if left untreated, are associated with adverse neurodevelopmental outcomes, including intellectual disability (ID). However, evidence addressing the role of neonatal thyroid hormones in the altered neurobiology underlying autism spectrum disorders (ASD), particularly among its subphenotypes, is limited. **Methods:** We conducted a population-based, case-control study among a sample of 4.5–9-year-old children born during 2000–2003 in Southern California. We examined neonatal thyroid-stimulating hormone (TSH) levels measured during routine newborn screening among children later diagnosed with ASD (n=518) or ID (n=145) and general population (GP) controls (n=399). TSH was further analyzed in relation to ASD subgroups of intellectual ability and onset type (early-onset ASD vs. ASD with regression) ascertained by expert review of developmental services records. Odds ratios (ORs) of the differences in TSH levels between ASD or ID status vs. GP controls were obtained from multivariate unconditional logistic regression. We examined neonatal TSH as continuous (ln-transformed) and as quartiles. **Results:** In adjusted logistic regression models, we found no association between continuous neonatal TSH levels and ASD (adj-OR: 1.00, 95%CI: 0.79-1.26) nor ID (OR=0.97, 95%CI: 0.70-1.34). Among ASD subphenotypes, we observed an inverse trend between neonatal TSH and odds of ASD with regression; ASD with regression was marginally associated with continuous TSH (adj-OR: 0.78, 95%CI: 0.55-1.09) and significantly associated with the highest quartile of TSH (adj-OR: 0.51, 95%CI: 0.26-0.98). The odds of ASD-noID were also lower with increasing TSH but this relationship was more modest and not significant. **Conclusions:** While there was little evidence that neonatal TSH is related to overall ASD risk, these findings suggest that neonatal TSH levels may be associated with particular subtypes of ASD defined by onset and intellectual disability. Given that thyroid deficiencies at birth are amenable to therapy, further scrutiny of the intersection of thyroid hormones and ASD is warranted, with attention to ASD subphenotypes.

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2 Association of Polychlorinated Biphenyls and Organochlorine Pesticides With Autism Spectrum Disorder in Jamaican Children

MacKinsey Bach, The University of Texas Health Science Center at Houston

Abstract:

Introduction: Polychlorinated biphenyls (PCBs) and organochloride (OC) pesticides are persistent organic pollutants (POPs) of public health concern that may play a role in autism spectrum disorder (ASD). Jamaicans may be at high risk for exposure to PCBs and OC pesticides as they have been detected in water, sediment, fauna, and shrimp across Jamaica. **Objectives:** To examine the associations of PCBs and OC pesticides with ASD among Jamaican children. **Methods:** We conducted an age- and sex-matched case-control study enrolling n=169 pairs of Jamaican children 2–8 years old. Socioeconomic status and food frequency questionnaires were completed by the parents/guardians of each child. We collected 2–3 mL of whole blood for genetic analysis and 4–5 mL of serum for analysis of PCBs and OC pesticides. For POPs with $\geq 30\%$ above the limit of detection (LoD), we replaced observations below LoD with $\text{LoD}/\sqrt{2}$ and calculated arithmetic and geometric means. We dichotomized concentrations at the 75th percentile and used conditional logistic regression models to assess the associations of these POPs with ASD. Finally, we conducted interactive models to explore possible interactions between POPs exposures and genotypes of three glutathione S-transferase (GST) genes in relation to ASD. **Results:** PCB-153, PCB-180, total PCB, and 4,4'-DDE (hexane fraction) had $\geq 30\%$ of observations above LoD. Using concentrations dichotomized at the 75th percentile, we found inverse associations between PCB-153 [adjusted MOR (95% CI) = 0.44 (0.23 -; 0.86)] and PCB-180 [adjusted MOR (95% CI) = 0.52 (0.28 -; 0.95)] concentrations and ASD. There were no associations between total PCB and 4,4'-DDE and ASD. We found a marginally significant interactive effect between PCB-153 and genotype of GSTM1 in relation to ASD (interaction term $P=0.0780$); those with the null (D/D) genotype had a different level of association [MOR (95% CI) = 1.82 (0.59-; 5.59)] compared to those with the homozygote (I/I) or heterozygote (I/D) genotype [MOR (95% CI) = 0.60 (0.33-; 1.10)]. **Conclusions:** We found that cases had lower serum concentrations of 4,4'-DDE compared to controls. Cases also had lower odds of having lipid-adjusted PCB-153 and PCB-180 concentrations $\geq 75\text{th}$ percentile compared to controls. Differences in dietary habits between cases and controls may play a role in these inverse findings. Furthermore, we reported a possible interactive effect between PCB-153 and GSTM1, which warrants further investigation.

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3 Parental Lifetime Occupational Exposures and Risk of Autism Spectrum Disorder in Offspring

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Abstract:

Bone-seeking toxicants can accumulate in bone, and lipophilic compounds can accumulate in fat after occupational exposure. Both of these can be released into the blood stream as bone and fat metabolize during pregnancy, and lipophilic compounds can be easily transferred to infants via breastmilk. There are also suggested pathways of male-mediated embryonic malformations via paternal occupational exposures. Although previous studies of parental occupation and ASD in offspring have used exposure estimates reported at or around the time of pregnancy and birth, linking parental occupational exposures to neurodevelopment requires data collection that spans several years and continues into infancy and early childhood. I will utilize population-based surveillance data from the Danish National Patient Registry (DNRP) to identify all ASD cases at least 5 years of age in Denmark from 1995 to 2018 and four sex- and birth-year matched controls with no prior diagnosis of any other developmental disorder or intellectual disability. These data will be linked to Medical Birth Registry records, along with parental records from the Danish Central Population Register. Parental occupation history from the age of 16 to 6 months after childbirth will be obtained from the Danish Pension Fund, and occupational exposures will be estimated using job exposure matrices (JEMs) developed by the Nordic Occupational Cancer Study for Denmark. I will then investigate lifetime, prenatal, and postnatal parental occupation to evaluate the impact of accumulation of persistent chemicals and risk of ASD diagnosis in offspring. I will also pilot test a study of parental occupational exposures and DNA methylation in neonatal blood spots. Data obtained from occupation history questionnaires will be used in conjunction with JEMs specific to the US to estimate cumulative occupational exposures in male participants. I will then evaluate the impact of these measures of cytosine-phosphate-guanine (CpG) methylation of genes reported as associated with adverse neurodevelopment.

4 Association Between Socioeconomic Status and Level of Adaptive Behavior Limitations in Children With Autism Spectrum Disorder: Results From a Population-based Study

Sarah Furnier, University of Wisconsin-Madison

Abstract:

There has been an increased emphasis on characterizing the variation in functioning and level of support needed for children with autism spectrum disorder (ASD), especially when developing DSM-V based classification systems; however, few epidemiologic studies of ASD include information beyond dichotomous case status. The goal of this study was to explore the association between level of functional impairment in children with ASD, as measured by adaptive behavior (AB) test scores, and socioeconomic status (SES). Cross-sectional data from the Autism and Developmental Disabilities Monitoring (ADDMM) Network from all sites contributing between study years 2000 and 2014 was pooled for analysis. This analysis is restricted to data for 13,332 8-year-old children with ASD for whom AB test scores and SES data were available. AB scores were based on population normative data and categorized as (1) average or above, (2) borderline, (3) mild limitations, or (4) moderate to profound limitations. Measures of SES included tertiles of census tract median household income (MHI), percent of adults in the census tract with a bachelor's degree (BACH), percent of families with children living below the poverty line (POV), and residence in a census tract with 20 percent or more of families living below the poverty line (POVAREA). Correlation analysis and polytomous logistic regression were used to analyze the association between SES and AB scores. In general, there were a higher proportion of children with low SES among those with mild or moderate to profound limitations relative to children with less significant limitations ($p < 0.0001$). Likewise, SES was significantly negatively correlated with AB score ($p < 0.0001$), with lower SES being associated with greater limitations. Polytomous logistic regression results revealed that low SES as measured by MHI, POV, and POVAREA was associated with greater odds of having moderate to profound AB limitations relative to having average or above AB scores ($p < 0.001$); effect estimates revealed a similar, but non-significant, association between BACH and AB limitations. These results suggest evidence of a relationship between lower SES and greater AB limitations. This association may stem from under diagnosis of ASD in lower SES children with milder AB limitations, or from susceptibility to more severe AB limitations in children with ASD and low SES, perhaps due to more limited access to early interventions or other unmet service needs.

5 Air Pollution, Neighborhood Deprivation, and Autism Spectrum Disorder in the Study to Explore Early Development

Laura McGuinn, Icahn School of Medicine at Mount Sinai

Abstract:

Background: Previous studies have identified associations between air pollution exposure and autism spectrum disorder (ASD); however, the extent to which neighborhood deprivation modifies these associations remains largely unknown. In order to address this limitation, we investigated the modifying role of neighborhood deprivation on the association between early life air pollution exposure and ASD using data from the Study to Explore Early Development. **Methods:** We used data from 674 clinically confirmed ASD cases and 855 population controls. Both cases and controls were born between 2003–2006 in one of the study areas and still resided there at 30–68 months of age. Roadway proximity was used to capture the mixture of chemicals from traffic-related air pollution. Daily particulate matter with diameter less than 2.5 μm (PM_{2.5}) predictions were estimated using a 1 km satellite-based exposure model and averaged over pregnancy and the first year of life. To characterize neighborhood deprivation, an index was created based on eight census tract-level socioeconomic status-related parameters. The continuous index was categorized into tertiles, representing low, moderate, and high deprivation. Logistic regression was used to estimate odds ratios (OR) and corresponding 95% confidence intervals (CI) for the associations between roadway proximity, PM_{2.5}, and ASD. Modification by neighborhood deprivation was assessed on both the additive and multiplicative scales. All models were adjusted for study site, year and month of birth, and maternal education, race/ethnicity, age, and smoking. **Results:** Overall, compared to controls, children with ASD were more likely to be boys, born preterm, and born to non-white, lower educated mothers. PM_{2.5} averages during the pregnancy period were 13.3 $\mu\text{g}/\text{m}^3$ in the highest deprivation group and 12.4 $\mu\text{g}/\text{m}^3$ in the low deprivation group. Neighborhood deprivation modified (P for interaction = 0.08) the association between PM_{2.5} exposure during the first year of life and ASD, with a stronger association for those living in high (OR=2.42, 95% CI: 1.20, 4.86) rather than moderate (OR=1.21, 95% CI: 0.67, 2.17) or low (OR=1.46, 95% CI: 0.80, 2.65) deprivation neighborhoods. **Conclusions:** These results provide evidence for an association between first year of life PM_{2.5} exposure and childhood ASD, and suggest children living in more deprived neighborhoods may be particularly vulnerable to pollution effects. This abstract does not necessarily represent the official positions of the CDC or the EPA.

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6 Migration or Ethnic Minority Status and Risk of Autism Spectrum Disorders and Intellectual Disability: a Systematic Review

Maki Morinaga, Karolinska Institutet

Abstract:

There is emerging evidence that migration and ethnic minority status are associated with risks of autism spectrum disorder (ASD) and intellectual disability (ID). However, the details of these associations and their underlying mechanisms remain unknown. This systematic review investigated whether associations are specific to ASD or ID (and/or to the severity of ASD or ID); whether any increased risks of ASD and ID results from migration-related or ethnically determined factors; and what mechanisms may explain these risks. A systematic literature search was conducted using Embase, Medline, and PsycINFO for studies that reported on proportion, prevalence, odds ratio, or relative risks of ASD and/or ID among migrants, descendants of migrants, and/or ethnic minorities. Risks of any ASD, ASD+ID, ASD-ID, and any ID were reviewed in relation to migration and ethnic minority status, with consideration to study quality. In addition, possible underlying mechanisms suggested in the included studies were summarized. In all, 35 unique studies were included in the systematic review. The summarized evidence indicated an increased risk of ASD+ID and a decreased risk of ASD-ID in migrants, descendants of migrants, and ethnic minorities. These associations appeared more pronounced among children of migrant mothers, those with origin in low-income countries, and among descendants of migrants. Data on ID was scarce but suggested an increased risk of severe/profound ID and a decreased risk of mild ID in some ethnic minorities. Suggested mechanisms explaining the increased risks of ASD+ID and severe/profound ID included environmental factors acting in utero and genetic factors, while ascertainment bias was proposed to account for the observed lowered risks of diagnosed ASD-ID and mild ID. We conclude that the increased risks of ASD+ID in migrants and descendants of migrants may be related to migration-related rather than ethnically determined factors.

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7 Risk Prediction in ASD: Machine Learning Techniques to Identifying Autism in the Stockholm Youth Cohort

Jessica Rast, Drexel University

Abstract:

Introduction: Often used in clinical practice, risk prediction involves the use of related variables and known associates to predict an outcome. Risk prediction is not common in ASD research but is readily found in other disciplines. Prediction of ASD before a formal clinical diagnosis could be useful given the effectiveness of early intervention. ASD is known to have both genetic and environmental components. A genetic component of ASD is demonstrated from familial studies indicating strong heritability. There are several suspected environmental risk factors of ASD, including obstetric complications, increased parental age, interpregnancy interval, maternal use of potentially teratogenic medications during pregnancy, gestational age, and environmental chemicals. The purpose of this study is to use Swedish health and population data registers to train and validate risk prediction models of ASD. Results will address the utility of these methods to correctly identify ASD when known risk factors and associations are measured. **Methods:** This study uses data from the Stockholm Youth Cohort, a record linkage study of residents of Stockholm County from 2001–2011 ages 0–17 years. Information on youth and their first-degree relatives was recorded prospectively and linked to health and other registries of Swedish residents. To examine the utility of risk prediction in ASD, we will develop several prediction models and compare them on key informative criteria. We will use multivariate logistic regression and machine learning techniques including classification and regression trees (CART), bootstrap aggregation (bagged) CART, and random forests. We will split the data into training and testing portions using five-fold cross-validation, which aids in assessing how well the prediction model generalizes to other data. To examine performance and utility of each model, we will consider the accuracy of the model build on training data to correctly categorizing persons in the testing dataset, Cohen’s Kappa, sensitivity and specificity, positive and negative predictive value, and receiver operating characteristic curves.

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8 Maternal Polycystic Ovarian Syndrome and Other Androgen-related Conditions, and Risk of Autism Spectrum Disorders in Progeny

Ran Rotem, Harvard School of Public Health

Abstract:

Background: Fetal exposure to elevated androgens is thought to contribute to ASD risk. However, current data relies heavily on measurement of in-utero androgen concentrations, which also reflect androgens produced by the fetus. Androgen homeostasis is altered in individuals with ASD, and thus in-utero androgen-excess may reflect adverse ASD-related neurogenesis that had already occurred rather than being a true risk factor for the disorder. An association between maternal androgen-related conditions and ASD risk could more directly implicate androgen as a causal factor, but available data are limited. **Objectives:** To examine the association between PCOS, the primary cause of hyperandrogenemia in premenopausal women, and ASD risk in progeny. **Methods:** The study included 437,222 singleton births (4,022 with ASD) occurring between 1999 through 2013 in a large Israeli health fund. Data on ASD diagnoses and maternal androgen-related conditions were obtained through 2016. Maternal conditions and ASD cases were identified through ICD-9 codes with further verification through review of medical records and laboratory results. Odds ratios (OR) and 95% confidence intervals (CI) were estimated using generalized estimating equation (GEE) models to account for multiple children per mother. Mediation analysis for multiple mediators was performed using natural effects models. **Results:** Children born to mothers diagnosed preconceptionally with PCOS (n=17,922) had higher odds of ASD compared with children born to mothers without this condition (OR=1.34, 95%CI: 1.16,1.54). Mediation analysis indicated statistically significant direct and indirect effects of PCOS on ASD risk. Elevated effects were also observed for other maternal conditions linked with hyperandrogenemia. **Conclusions:** Results suggest a link between maternal androgen-related conditions and ASD risk in progeny, and additionally suggest that the risk is largely independent of other co-morbidities commonly associated with androgen excess. Findings provide some support for a possible direct involvement of maternal hyperandrogenemia in ASD etiology. Alternatively, the findings could also reflect shared genetic and environmental factors that affect maternal androgen homeostasis and fetal neurodevelopment through independent mechanisms.

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9 Parental age as a Risk Factor for Autism: Effect of Etiology or Socioeconomic Status

Eric Rubenstein, Waisman Center

Abstract:

Background: Older parental age is consistently seen to increase offspring risk of autism, yet it is not fully understood whether this is a result of biological mechanisms associated with reproduction in older ages or a result of differences in socioeconomic status (SES) related to having children at older ages. Our objective was to replicate past findings of increased odds of autism to older mothers or fathers and evaluate patterns by SES to clarify social and biologic effects using data from the Autism and Developmental Disabilities Monitoring Network (ADDM) and population birth records. **Methods:** ASD cases were identified from the ADDM Network study years 2006–2014 and we created a “quasi-control” group using publicly available birth records from children born in the same year in the same county. If county-level birth records were not available due to small county size, we took a random stratified sample from the state level to correspond with demographic characteristics of the county. Parental age/socioeconomic information was taken from the birth certificate. We ran logistic regression adjusted for child year of birth, site, maternal education, race/ethnicity, and other parent’s age. **Results:** Our final sample was 12,339 children with ASD and 1.34 million children from population birth certificates who had age listed for both parents. Also, 1,591 children with ASD and 276,723 children from population birth certificates had only mother age listed. 4.2% of the ASD cohort and 2.7% of the birth record cohort had mothers ≥ 40 years old. 12.6% of the ASD cohort and 9.7% of the birth record cohort had fathers ≥ 40 years old. Odds of child ASD in mothers ≥ 40 years old were 1.79 times that of mothers 25–29 years old. We saw sub-additive multiplicative effects if both parents were older. We saw increasing odds with increasing age across strata of maternal education, race, and birth order. **Conclusions:** Older maternal age and older paternal age independently associated with increased odds of ASD. We found sub-additive interaction for having both parents older, meaning having both parents older did not impart excess risk compared to just having one older parent. Trends of increasing odds with increasing age are consistent across race, education, and birth order. Our results suggest that the trend of increasing odds with increasing parent age is consistent across SES factors, with groups with indicators for high SES having higher initial odds for ASD.

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10 Perinatal Factors Associated With Autism Spectrum Disorder in Jamaican Children

Sepideh Saroukhani, The University of Texas Health Science Center at Houston, School of Public Health

Abstract:

Background and aim: Autism Spectrum Disorder (ASD) is a neurodevelopmental disorder mostly believed to stem from complex genetic-environmental interactions. We investigated the possible association of perinatal factors including mode of delivery, low birth weight (LBW), and preterm birth with ASD in Jamaican children. **Methods:** Using data from 343 pairs of age (± 6 months) and sex-matched ASD cases and typically developing controls who were enrolled in the Epidemiological Research on Autism in Jamaica (ERAJ) study during 2009–2018, we performed conditional logistic regression to assess the possible association of each perinatal factor with ASD while controlling for potential confounders. Additionally, we explored potential interactions between the perinatal exposures and other covariates in relation to ASD. **Results:** While we found a significant unadjusted association between Cesarean delivery and ASD (matched odds ratio [MOR] and 95% confidence interval [95% CI]: 1.79 [1.23-2.60], $P = 0.002$), our multivariable analysis findings suggested that the parish of residence may be an effect modifier for the association between Cesarean delivery and ASD in Jamaican children. Specifically, for children who lived in Kingston parish (mainly urban), Cesarean delivery was significantly associated with ASD after adjusting for the age of the parents at the child's birth (adjusted MOR [95% CI]: 2.34 [1.19-4.61], $P=0.013$), whereas this association was not significant for children from other parishes with a higher percentage of rural residents (adjusted MOR [95% CI]: 0.94 [0.52-1.69], $P = 0.824$). Additionally, although not statistically significant, the association between LBW and ASD appeared to be modified by the household socioeconomic status (SES) in Jamaica, after adjusting for the age of the mother at the child's birth (adjusted MOR [95% CI]: 1.79 [0.89-3.64], $P = 0.10$ for low SES, and 0.64 [0.30-1.36], $P = 0.248$ for high SES families). Our findings do not support a significant association between preterm birth and ASD after adjusting for the age of the parents at the child's birth and SES (adjusted MOR [95% CI]: 1.21 [0.66-2.20], $P = 0.539$). **Conclusions:** Our findings suggest that the parish of residence may be an effect modifier of the association between cesarean delivery and ASD in Jamaican children. Also, SES may be an effect modifier of the association between LBW and ASD in Jamaica. These findings require replication in future studies.

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11 High Resolution Mass Spectrometry for Biomarker and Risk Factor Discovery

Nathaniel Snyder, Drexel University

Abstract:

Hypothesis-based epidemiologic study of candidate prenatal risk factors for autism spectrum disorder (ASD) commonly utilize exposure or exposure-response biomarkers obtained from biospecimens collected in the pre- or peri-natal window. When these targeted analyses utilize liquid chromatography-high-resolution mass spectrometry (LC-HRMS) on modern instruments, the picture of the molecular contents of the sample can often be expanded by semi-quantitative description of the wider chemical space (metabolomics/exposomics), which may facilitate the development of hypothesis-agnostic, discovery type analyses. We previously conducted targeted analyses for four exposure or exposure-response biomarkers using LC-HRMS in two different cohorts across four sample types and with five classes of targeted analytes using hybrid targeted/untargeted metabolomics. In the EARLI cohort, we quantified the sex steroid and phthalate metabolite content by two separate methods in meconium samples (n=193) as well as metabolites of prostaglandin E2 from maternal urine (n= 547 across multiple gestational visits). In addition, in maternal serum (n=1,002 across multiple gestational visits) and newborn blood spots (n=400), we quantified polyunsaturated fatty acids (PUFAs) from a case-control study built from the state of California registry and biobank. All experiments were conducted on a Q Exactive Plus high-resolution mass spectrometer coupled to an Ultimate 3000 high-pressure liquid chromatography in the same laboratory by blinded analysts. After targeted analysis was conducted, data was re-interrogated with untargeted metabolomics pipelines. Targeted assays with known performance characteristics provided quantitative abundance on select analytes. Simultaneously, semi-quantitative relative abundance was collected on around 10,000–14,000 features per experiment, with number of features depending on the biosample and method of analysis. Putative identification was conducted by database searching. Confirmatory identification for select analytes was conducted by LC-MS/HRMS, and elution time matching with an authentic standard. Some targeted analytes, including PUFAs, were detected by other analytical methods in other sample types. Other molecules, including unconjugated testosterone, were only detected in targeted analysis. This allowed us to compare findings across some, but not all, studies.

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12 Trimester-specific Variation in Air Quality and Risk for Autism Spectrum Disorder: a Natural Experiment

Peng-Chou Tsai, Johns Hopkins Bloomberg School of Public Health

Abstract:

Background: Prenatal air pollution exposure (PNAPE) has been associated with a broad range of neurodevelopmental outcomes. Ten reports from the U.S. have identified associations between PNAPE and autism spectrum disorder (ASD). To our knowledge only three studies outside the U.S. have examined the relationship between PNAPE and risk for ASD. Publications from European cohorts have reported no association of air pollution exposure with ASD. These studies did not employ gold standard ASD assessments, raising the possibility of misclassification of case status. Application of varied assessment methods at different ages compounded the potential for bias due to misclassification of disease. These studies provide evidence on associations between air pollution exposure and ASD. However, due to study design limitations, a causal relationship is far from certain. Moreover, studies of PNAPE in regions with extremely high levels of air pollution are lacking. By studying children born around the 2008 Beijing Olympics and Paralympics, the proposed study provides a unique opportunity to examine trimester-specific variation in air quality and risk for ASD. **Objectives:** 1) Estimate population-based prevalence of ASD in Beijing City among children who were in utero before, during, and after the Olympic period. 2) Assess time-window-specific PNAPE effects on ASD. 3) Investigate the extent to which the effect of PNAPE on ASD and ASD traits is mediated by birthweight and gestational age at birth. **Methods:** Participants will be children born between 4/1/2008 and 7/31/2009, whose mothers resided in two districts of Beijing City 12 months before the subject child was born. We are proposing a population-based case identification approach where children in the study defined birth cohort are eligible for participation. According to the birth registry, there were 18,887 live births of infants who had gestation between 4/1/2008 and 7/31/2009 in the two selected study districts. Initial screening for ASD will involve children from three recruitment sources: 1) elementary schools, 2) the Beijing Disabled Persons' Federation, and 3) community care centers. Face-to-face clinical visits will be conducted with families of children who screen ASD positive on the study screening tools, as well as a randomly selected sample of children who screen negative. Case status determination will be based on an operationalization of the DSM-5 ASD criteria. **Conclusion:** We plan to launch this study in May 2019.

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13 In Utero Exposure to Tobacco Smoke and Risk of Autism Spectrum Disorder and Attention-Deficit/Hyperactivity Disorder in the Third Generation

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Abstract:

Background: Animal experiments indicate that environmental factors can alter gene expression to induce multigenerational transmission of biological traits to subsequent generations through the germline. However, there is very little data on such effects in humans. Cigarette smoke is one exposure that is known to alter germline DNA methylation patterns, but only a single study has investigated the association between grand-maternal smoking in pregnancy and grandchild's diagnosed autism using data from the Avon Longitudinal Study of Parents and Children (ALSPAC). **Objectives:** To examine the associations between grandmother smoking while pregnant and risk of autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD) in her grandchildren. **Methods:** We analyzed data reported by nurses in The Nurses' Health Study (NHS) II, the participants of which were born between 1946 and 1964. In 1999, nurses (F1) were asked whether their mother (F0) smoked during her pregnancy with them. ASD and ADHD cases were identified according to the nurses' report of whether or not they had ever had a child (F2) diagnosed with ASD (2009) or ADHD (2013). Data were analyzed using cluster-weighted generalized estimating equations with a logit link. Models were adjusted for several potential confounders. Additionally, sensitivity analyses were conducted by repeating our main analyses adjusting for potential mediators (i.e., F1 smoking during pregnancy with F2). **Results:** For ASD, N=44,660 F1 mothers had data on exposure, outcome, and confounders, and for ADHD, N=42,218 F1 mothers had complete data. For both outcomes, the prevalence of F0 smoking during the pregnancy with the F1 nurses was similar (24.9% and 24.7% for ASD and ADHD outcomes, respectively). Of 100,670 and 95,218 F2 children, 1,272 (1.26%) were diagnosed with ASD and 7,173 (7.53%) were diagnosed with ADHD. Grand-maternal smoking during the pregnancy with the nurses was associated with an increased risk of ADHD among the grandchildren with adjusted odds ratio (aOR) of 1.18 (95% CI, 1.11-1.27), whereas an association was not observed between F0 smoking during the pregnancy with F1 and a risk of ASD among the F2 generation (aOR = 0.97; 95% CI, 0.85-1.12). Controlling for the F1 level potential mediators did not substantially change the findings. **Conclusions:** Maternal prenatal exposure to smoking is associated with an increased risk of ADHD, but not with ASD.

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14 Data Science Training in Environmental Health Sciences: Resources, Challenges, and Needs

NIEHS DERT Data Science Working Group, National Institute of Environmental Health Sciences

Abstract:

With rapidly developing technology and more efficient data collection procedures, environmental health scientists are now collecting vast amounts of data. These data, often referred to as “big data,” can be large, complex, multidimensional, and diverse. Environmental health data are associated with basic, translational, clinical, epidemiological, social, behavioral, environmental, or informatics research questions. Such data types may include imaging, phenotypic, genotypic, molecular, clinical, behavioral, environmental, and many other types of biological and biomedical data. Appropriate tools, access to quality datasets, and training are needed to harvest the wealth of information contained in these data to advance our understanding of the role of the environment in human health and disease.

The National Institute of Environmental Health Sciences (NIEHS) is interested in learning more about your experiences as NIEHS trainees and junior scientists in environmental health sciences research regarding your interaction with “big data” and data science training.



Biographies

Alan Brown
Columbia University

Alan S. Brown, M.D., M.P.H., is professor of psychiatry and epidemiology at Columbia University and director of the program in birth cohort studies at New York State Psychiatric Institute. . Brown is a leader in collaborative birth cohort studies of prenatal, perinatal, and other early life exposures in relation to risk of neuropsychiatric disorders in offspring, including autism, schizophrenia, bipolar disorder, major depression, and attention deficit hyperactivity disorder. His seminal findings include the identification of maternal organic pollutants, infections, inflammatory markers, micronutrient deficiencies, and smoking as risk factors for neuropsychiatric outcomes. He is principal investigator of research investigations in large and prominent birth cohort studies, including the Finnish Prenatal Studies (FiPS), which is based on a large, national birth cohort. He has published widely on these topics in peer-reviewed journals, has received numerous research grants from the NIH including the NIEHS and others. He has also been the recipient of several scientific awards including the A.E. Bennett Research Award and has served extensively on NIH study sections. He is an associate editor of the American Journal of Psychiatry, is on the editorial board of Schizophrenia Bulletin, and is a fellow of The American College of Neuropsychopharmacology.

Amy Kalkbrenner
University of Wisconsin-Milwaukee

Amy Kalkbrenner, Ph.D., M.P.H., uses epidemiologic methods to study how exposures to environmental pollutants during pregnancy cause poor birth outcomes (such as preterm birth) or neurodevelopmental disorders, like autism. She focuses on airborne exposures, such as traffic-related pollutants like fine particulate matter (PM_{2.5}), the hundreds of airborne metals and volatile organic compounds known as air toxics or hazardous air pollutants, and tobacco smoke. She brings concepts of exposure mixtures, etiologic heterogeneity, and causal inference into her work, all with the goal of ultimately improving the public's health. Kalkbrenner received her master of public health from the University of California, Berkeley, her doctorate in epidemiology from the University of North Carolina She now serves as associate professor at the Zilber School of Public Health at the University of Wisconsin-Milwaukee.

Youssef Oulhote
University of Massachusetts Amherst

Youssef Oulhote, Ph.D., is assistant professor in the department of biostatistics and epidemiology at the University of Massachusetts at Amherst and visiting research scientist in the department of environmental health at Harvard T. H. Chan School of Public Health. Oulhote received his engineering degree from the National Institute of Veterinary and Agricultural Sciences in Morocco, a master's degree in quantitative risk assessment from the AgroParisTech Engineering School in Paris, and a doctorate from the French National School of Public Health. As an epidemiologist, Oulhote's research focuses on the health effects of early life exposures to metals (e.g. mercury, lead, and manganese) and endocrine disruptors (e.g. PBDEs, PFAS, and phthalates), with an emphasis on children's cognitive and behavioral functions. Oulhote also investigates the application of machine learning techniques within a causal inference framework. Finally, his work explores the interplay of environmental, nutritional, and social factors, and how these exposures interact to impact population health.

Nathaniel Snyder
Drexel University

Nathaniel Snyder, M.P.H, Ph.D., is an assistant professor at the A.J. Drexel Autism Institute at Drexel University. His current work focuses on identifying and measuring modifiable risk factors for autism spectrum disorder (ASD). The long-term goals of this work are to bridge population and individual-level scientific approaches and develop a public health approach to prevention of ASD. Snyder studied Biochemistry at the University of Maryland and trained at the National Institutes of Health. His Ph.D. thesis in pharmacology at the University of Pennsylvania concerned analytical measurements of low-abundance biological molecules using liquid chromatography-mass spectrometry (LC-MS). Also completed at the University of Pennsylvania, Snyder's MPH work investigated non-invasive biomarkers of asbestos exposure and contributed to the Penn Superfund Research and Training Program. Snyder has published and presented academic works on analytical chemistry, metabolism, inflammation, and environmental exposure assessment.

Current research projects include studies of environmental exposures, metabolic pathways involved in neurodevelopment, and molecular mechanisms that may mediate ASD. Additional projects include fundamental work on improving sample collection and analysis, as well as refining epidemiological trial design using laboratory measurements. He staffs the Exposure Science Lab at the Autism Institute.

Dheeraj Rai
University of Bristol

Dheeraj Rai, Ph.D., is a clinical academic psychiatrist and lead of the neurodevelopmental disorders research group at the Centre for Academic Mental Health. His clinical work involves providing psychiatric advice and care to adults with intellectual disabilities, and autism assessments for adults with and without intellectual disabilities. The work of his research group focuses on three broad areas: Understanding the prenatal and early life determinants of autism and other neurodevelopmental conditions, understanding the adult outcomes of autism and other neurodevelopmental conditions (particularly mental health comorbidity) and interventions that may improve the mental health and quality of life in people with autism.

Much of the work is based within large longitudinal cohorts including the Avon Longitudinal Study of Parents and Children (ALSPAC), the Stockholm Youth Cohort and other population-based studies. Because confounding is a major problem in observational studies, his group's work has increasingly focused on the application of methods that can strengthen causal inference to answer clinically important questions. These include propensity score methods, mendelian randomization, instrumental variable methods, sibling designs, and negative control designs.

He is also interested in randomized controlled trials of interventions that may improve mental health outcomes and quality of life in autistic adults. Recruitment and retention in such studies is often challenging. He is interested in methodologies to improve the design of such studies and how this can be done in genuine partnership with the autistic community.

His work is interdisciplinary and involves a wide range of collaborative partnerships with colleagues in Bristol and in many different parts of the UK and internationally.



Participant List

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**Environmental
Epidemiology of Autism
Risk Network (EEARN)
Meeting**

Montreal, Canada

National Institute of Environmental Health Sciences

National Institutes of Health • U.S. Department of Health and Human Services